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Hypoalbuminemia in Acute Illness: Is There a Rationale for Intervention?

A Meta-Analysis of Cohort Studies and Controlled Trials

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Objective
To determine whether hypoalbuminemia is an independent risk factor for poor outcome in the acutely ill, and to assess the potential of exogenous albumin administration for improving outcomes in hypoalbuminemic patients.

Summary Background Data
Hypoalbuminemia is associated with poor outcomes in acutely ill patients, but whether this association is causal has remained unclear. Trials investigating albumin therapy to correct hypoalbuminemia have proven inconclusive.

Methods
A meta-analysis was conducted of 90 cohort studies with 291,433 total patients evaluating hypoalbuminemia as an outcome predictor by multivariate analysis and, separately, of nine prospective controlled trials with 535 total patients on correcting hypoalbuminemia.

Results
Hypoalbuminemia was a potent, dose-dependent independent predictor of poor outcome. Each 10-g/L decline in serum albumin concentration significantly raised the odds of mortality by 137%, morbidity by 89%, prolonged intensive care unit and hospital stay respectively by 28% and 71%, and increased resource utilization by 66%. The association between hypoalbuminemia and poor outcome appeared to be independent of both nutritional status and inflammation. Analysis of dose-dependency in controlled trials of albumin therapy suggested that complication rates may be reduced when the serum albumin level attained during albumin administration exceeds 30 g/L.

Conclusions
Hypoalbuminemia is strongly associated with poor clinical outcomes. Further well-designed trials are needed to characterize the effects of albumin therapy in hypoalbuminemic patients. In the interim, there is no compelling basis to withhold albumin therapy if it is judged clinically appropriate.

The normal serum concentration of albumin in healthy adults is approximately 35 to 50 g/L. Diminished circulating level of albumin—hypoalbuminemia—is common in seriously ill patients. For instance, the reported frequency of hypoalbuminemia, defined as a serum albumin concentration of less than 34 g/L, was 21% at the time of admission in adult hospitalized patients.[1] After admission, worsening of existing hypoalbuminemia and development of de novo hypoalbuminemia are both frequently encountered.[2]

The increased likelihood of poor outcomes such as mortality, morbidity, and prolonged intensive care unit (ICU) and hospital stay in acutely ill patients with hypoalbuminemia is well recognized.[3,4] Because of its importance as an outcome predictor, serum albumin level has been added as one of the component parameters in the Acute Physiology and Chronic Health Evaluation (APACHE) III score.[5] The association between hypoalbuminemia and poor outcomes has long motivated clinicians in administering exogenous albumin to hypoalbuminemic patients,[4] and hypoalbuminemia is a licensed indication for human albumin in the United States and other countries. However, the appropriateness of this practice has been challenged on the basis of insufficient evidence to support its efficacy.[4,6]

At the heart of the controversy is causality—whether hypoalbuminemia directly contributes to poor outcomes, in which case albumin replacement therapy might bestow benefit, or merely serves as a marker for other "upstream" pathologic processes such as malnutrition or inflammation,

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in which case exogenous albumin might be ineffective in altering the clinical course of the patient. Two types of currently available evidence might help elucidate the appropriateness of albumin replacement therapy for hypoalbuminemia: results from multivariate analysis of cohort study data collected for the purpose of evaluating the relationship between albumin level and outcome specifically in acutely ill patients, and findings of controlled trials evaluating the effects of correcting hypoalbuminemia on morbidity. Such evidence has not previously been systematically reviewed.

Multivariate analysis is crucial to an epidemiologic inquiry into causality, since it can directly address whether other risk factors satisfactorily explain the hypoalbuminemia effect and can provide more accurate estimates for the strength of the hypoalbuminemia effect and the dose-response relationship between endogenous serum albumin level and outcome. Lack of detectable confounding, strength of association, and dose-response relationship, as well as plausible biologic mechanisms, are the principal epidemiologic criteria for evaluating causality.[7] Multivariate analysis has been reported on voluminous data generated in cohort studies examining the effects of hypoalbuminemia on a variety of clinical outcomes in the acutely ill. The preponderance of this evidence has been published only recently.

Two recent meta-analyses failed to detect a significant effect of albumin administration on survival in randomized controlled trials of hypoalbuminemic patients.[8,9] However, in these trials the numbers of patients enrolled were small. Furthermore, the reported mortality rate in the control group was only 10% to 12%. Consequently, mortality was a relatively insensitive endpoint in this patient population. Complications, on the other hand, are substantially more frequent than deaths, and thus morbidity may serve as a more sensitive indicator for the effects of administered albumin. In addition, morbidity is a major concern of patients.[10]

Through systematic review, we have endeavored to identify all cohort studies with multivariate analysis of serum albumin level as an outcome predictor and all controlled trials on correction of hypoalbuminemia. We here report the results of a meta-analysis encompassing both types of investigations.

MATERIALS AND METHODS

Inclusion Criteria

For inclusion, cohort studies must have focused on serum albumin as an outcome predictor in the acutely ill and entailed multivariate analysis by methods such as logistic regression or Cox proportional hazards regression. No restrictions were placed on the types of acute illnesses or outcomes addressed. Thus, we adopted broad inclusion criteria. Views differ as to the optimal scope for meta-analyses; however, broad meta-analyses have been advocated on the basis of their statistical power and generalizability.[11]

Published and unpublished prospective controlled trials were included if they were designed to evaluate the effects of correcting existing hypoalbuminemia in the acutely ill. Morbidity data must have been available. Trials of hypoalbuminemia prevention in patients with normal serum albumin levels at study entry were not included. A randomized design was not required. The control group must have received either crystalloid or no albumin. Trials comparing albumin with synthetic colloids, blood products, or plasma protein fraction as the control regimen were not included.

Search Techniques

Relevant studies were sought without language restriction by computer searches of the MEDLINE and EMBASE bibliographic databases, the Cochrane Controlled Trials Register, and the Cochrane Medical Editors Trial Amnesty of unpublished trials. Additional Internet-resident resources such as conference reports, abstracts, reference compilations, and full-text journal articles were located using the Altavista, Northernlight, Hotbot, Excite, and Google search engines. We searched the *Journal of the American Medical Association*, the *New England Journal of Medicine*, *The Lancet*, and the *British Medical Journal* by hand for the period from January 1990 to May 2002 and *Index Medicus* for the years 1940 through 1965. We also consulted the authors of published controlled trial reports related to albumin and the medical directors of albumin suppliers and examined the reference citations from completed reviews and protocols in the Cochrane Database of Systematic Reviews, other meta-analyses, review articles, and reports of controlled and uncontrolled studies involving albumin.

Data Collection

Two investigators independently selected studies and extracted data. Disparities in selection and extraction decisions were resolved through discussion. In controlled trials, complications were scored on an intention-to-treat basis.

Statistical Analysis

Individual study results were expressed as odds ratios (OR) with 95% confidence intervals (CI). To allow for between-study statistical heterogeneity, OR estimates were quantitatively combined under a random effects model. OR values more than 1 signify an increased probability of poor outcome.

Most multivariate analyses from cohort studies were performed by either logistic regression or Cox regression. Exponentiated coefficients from these two types of analysis provide an OR and hazard ratio, respectively, for the outcome of interest. These two effect size metrics, though distinct, have been shown both theoretically and empirically to be similar in magnitude under a range of conditions.[12,13] We use the term OR to denote both these effect size measures. Logistic regression and Cox regression models can

accommodate both continuous variables such as serum albumin level or body mass index and binary indicator variables such as the presence of chronic renal disease or diabetes. The OR corresponding to the impact of hypoalbuminemia on a particular endpoint is adjusted during the estimation process to account for the effects of the other explanatory model variables.

In some included cohort studies OR was reported on the basis of broad serum albumin cutoffs (e.g., <35 vs. ≥ 35 g/L). In such cases we used the provided OR value and estimates of the median serum albumin values within the two cutoff ranges to calculate OR for each 10-g/L decrement in serum albumin.[14] The median values were wherever possible estimated from within-study data on the distribution of serum albumin concentrations and otherwise from comparable studies in the same or similar clinical indications. In a few cohort studies OR values for each of several serum albumin levels were supplied, and OR per 10-g/L serum albumin decline was estimated by weighted least-squares regression.[15] When *P* values were the only measures of precision reported, the test-based CI was calculated.[14] For cohort studies we employed the META computer program[16] to calculate pooled estimates of OR and CI and evaluate heterogeneity.

For prospective controlled studies, the primary outcome measure was the OR for occurrence of one or more complications in individual patients. The METAN computer program[17] was used to calculate OR and CI for individual studies, assess heterogeneity, and derive pooled estimates of OR and CI across studies. Because of pre-existing evidence indicating a dose-response relationship between albumin level and outcome,[18] the analysis plan also called a priori for an evaluation of outcome in relation to the mean peak serum albumin level attained during albumin therapy. This evaluation was performed by meta-analysis regression[19] using the METAREG program.[20]

Publication bias in controlled trials was assessed by the method of Egger et al[21] using the METABIAS program.[22] The methodologic quality of controlled trials was appraised on the basis of blinding, the presence of morbidity as a study endpoint, and between-group crossover by one or more patients. In the case of randomized controlled trials, the allocation concealment method was classified as adequate, inadequate, or unclear.[23]

RESULTS

Cohort Studies

Ninety cohort studies fulfilling the inclusion criteria were identified (Table 1).[1,2,18,24–110] The total number of patients in the 90 studies was 291,433 and the median number of patients per study was 281 (range 32–54,215). Forty-nine of the studies, with 200,413 patients, representing 69% of the total patient population, were published since 1998. Thirty studies involved hospitalized patients in general, 11 cardiac surgery, 12 noncardiac surgery, and 37 renal dysfunction. The total numbers of patients in the respective categories were 27,730, 39,080, 65,828 and 158,795. The median patient age across all included studies was 60 years (range 10–89), and the median percentage of males in the study populations was 55% (range 26–100%).

Forty-one included studies were prospective and 45 were retrospective. Four studies involved both prospective and retrospective components. Five studies were multicenter investigations.

Multivariate analysis was conducted by logistic regression in 40 studies, Cox regression in 36, and both in 1. OR and CI could be extracted or derived from the reports of 67 studies. The remaining 23 studies either did not supply the necessary data or employed a type of multivariate analysis that does not yield an OR estimate. Hence, data from these 23 included studies could not be quantitatively combined.

The median number of covariates (i.e., variables in addition to albumin evaluated for inclusion in the multivariate models) per study was 11 (range 1–124). Mortality was an endpoint of 66 studies, morbidity of 27, hospital stay of 9, ICU stay of 3, resource utilization (i.e., ventilatory support, transfusion or hospitalization) of 9, treatment failure of 2, quality of life of 1, and overmedication of 1. A single endpoint was subjected to multivariate analysis in 71 studies, 2 endpoints in 14 studies, 3 in 3 studies, and 5 in 2 studies. The total number of multivariate analyses among all 90 studies was 118.

The strength of association between serum albumin and outcome was reported for 26 final multivariate models. The median rank of albumin, from strongest to weakest predictor, versus all other covariates included in the final models was 2 (range 1–11). The median number of covariates in these final models, not counting albumin itself, was 5 (range 1–24). Thus, albumin was among the most powerful outcome predictors.

In eight analyses both univariate and multivariate OR estimates were provided for the association between serum albumin and outcome. In three analyses the multivariate exceeded the univariate estimate by an average of 38%, while in the other five analyses the univariate estimate was larger by a mean of 24%. These observations confirm that adjustment for the effects of covariates can result in substantially altered effect size estimates.

Mortality

OR and CI estimates for mortality associated with a 10-g/L fall in serum albumin were obtained for 53 studies (Fig. 1). The pooled OR for these trials was 2.37 (CI 2.10–2.68). Thus, the odds of death were increased by 137% with each 10-g/L decline in serum albumin, and the effect was statistically significant. Similarly, based on pooling within clinical indications, statistically significant increases in mortality odds of 102%, 116%, 180%, and 148% were observed for the hospitalization (OR 2.02; CI 1.52–2.70), cardiac surgery (OR 2.16; CI 1.47–3.16), noncardiac

Table 1. CHARACTERISTICS OF COHORT STUDIES TRIALS DESIGNED TO EVALUATE EFFECTS OF HYPOALBUMINEMIA ON OUTCOME

Study	Patients	Clinical Setting	Design	Analysis	Covariates
Hospitalization					
Harvey et al, 1981[25]	282	Critically ill and/or malnourished patients	RS	DA	12
Agarwal et al, 1988[26]	80	Consecutive elderly patients	PS	LR	9
Levkoff et al, 1988[27]	1,756	Elderly hospitalized patients	RS, PS	RP	31
Trzepacz et al, 1988[28]	108	Consecutive liver transplantation candidates	PS	DA	5
Bladé et al, 1989[29]	180	Multiple myeloma	RS	CR	14
Sullivan et al, 1990[34]	110	Consecutive admissions to Veterans Administration hospital geriatric rehabilitation unit	PS	DA	53
Cherng et al, 1991[35]	265	Multiple myeloma	MC, RS	CR	18
Levis et al, 1991[36]	342	Chronic lymphocytic leukemia	RS	CR	18
Herrmann et al, 1992[1]	15,511	Patients > 40 y of age	RS	LR	6
Burr et al, 1993[38]	200	Patients admitted to rehabilitation center within 1 y of spinal cord lesion	PS	ANOVA	12
Ferguson et al, 1993[39]	81	Hospitalized elderly nursing home residents	PS	LR	2
McEllistrum et al, 1993[41]	148	Consecutively discharged geriatric Veterans Administration hospital patients	RS	MR	1
Sirott et al, 1993[44]	284	Metastatic malignant melanoma	RS	WR	54
Toledo et al, 1993[45]	185	Spontaneous bacterial peritonitis in cirrhotic patients treated with cefotaxime	RS	LR	50
Espinosa et al, 1995[49]	292	Advanced non-small cell lung cancer	RS	CR	8
Violi et al, 1995[51]	165	Cirrhosis	PS	CR	8
McCluskey et al, 1996[2]	348	Consecutive critically ill patients	RS	LR	1
Gariballa et al, 1998[65]	201	Stroke	PS	CR	13
Incalzi et al, 1998[69]	370	Patients > 70 y of age in acute-care university hospital	PS	LR	11
Marinella and Markert, 1998[71]	144	Consecutive hospitalized patients 60 y of age or older	PS	ANOVA	1
Deschènes et al, 1999[77]	140	Cirrhotic patients without initial infection	PS	LR	7
Axdorph et al, 2000[83]	145	Patients > 15 y of age with Hodgkin's disease	RS	CR	14
Dharmarajan et al, 2000[86]	121	*Clostridium difficile* colitis	RS	LR	21
Dhiman et al, 2000[87]	288	Consecutive patients with fulminant hepatic failure	PS	LR	7
Oki et al, 2000[91]	1,594	Kawasaki disease	PS	LR	7
Leung et al, 2001[98]	340	Patients referred to hospital diabetic foot clinic	RS	LR	5
Rozzini et al, 2001[99]	840	Patients ⩾ 75 y consecutively admitted to acute care unit	PS	CR	5
Walter et al, 2001[103]	2,922	Hospitalized patients > 70 y with medical illnesses	PS	LR	15
Modawal et al, 2002[106]	145	Ventilator-dependent patients	RS	LR	10
Tincani et al, 2002[109]	143	Venous thromboembolism	PR	LR	5
Cardiac Surgery					
Rich et al, 1989[30]	92	Consecutive patients ⩾ 75 y undergoing cardiopulmonary bypass	RS	MR	5
Magovern et al, 1996[56]	2,802	Consecutive coronary artery bypass graft surgery patients	RS, PS	LR	124
Magovern et al, 1996[57]	2,033	Isolated coronary artery bypass graft	RS	LR	13
Rady et al, 1997[61]	1,461	Adult cardiovascular ICU patients	PS	LR	19
Rady et al, 1997[60]	2,743	Adult cardiovascular ICU patients	PS	LR	3
Ryan et al, 1997[62]	324	Adults in cardiovascular ICU ⩾ 14 d	RS	LR	18
Göl et al, 1998[66]	9,352	Open heart surgery	RS	LR	19
Rady et al, 1998[75]	1,157	Elderly cardiothoracic ICU patients	PS	LR	27
Engelman et al, 1999[78]	5,168	Coronary artery bypass graft, valve operations or both	PS	LR	17
Rady and Ryan, 1999[81]	11,330	Cardiothoracic ICU patients	RS	LR	22
Bashour et al, 2000[84]	2,618	Coronary artery bypass graft and/or valve surgery	PS	CR, LR	9
Noncardiac Surgery					
Buzby et al, 1980[24]	261	General surgery, gastrointestinal surgery	RS, PS	DA	13
Altomare et al, 1990[31]	70	Enterocutaneous fistulae	RS	LR	2
Lai et al, 1990[32]	86	Consecutive patients undergoing emergency surgery for severe acute cholangitis	RS	DA	22
Guijarro et al, 1996[54]	675	Renal transplant recipients	RS	CR	6
Pacelli et al, 1996[58]	604	Intra-abdominal infections	RS	LR	12

(*continues*)

RS, retrospective; PS, prospective; MC, multicenter; LR, logistic regression; CR, Cox regression; DA, discriminant analysis; MR, multiple regression; ANOVA, analysis of variance; RP, recursive partitioning; WR, Weibull regression; ICU, intensive care unit; USRDS, United States Renal Data System; CAPD, continuous ambulatory peritoneal dialysis; ESRD, end-stage renal disease.

Table 1 ***(continued).***

Study	Patients	Clinical Setting	Design	Analysis	Covariates
Noncardiac Surgery					
Friedenberg et al, 1997[59]	64	Percutaneous endoscopic gastrostomy	PS	LR	9
Hedström et al, 1998[67]	437	Femoral neck fractures	RS	LR	7
Becker et al, 1999[76]	232	Kidney-pancreas transplant	RS	CR	1
Gibbs et al, 1999[18]	54,215	All noncardiac surgery	MC, PS	LR	61
Gerhards et al, 2000[88]	112	Consecutive patients undergoing resection for hilar cholangiocarcinoma	RS	LR	8
Nair et al, 2000[90]	112	Consecutive patients undergoing resection for hilar cholangiocarcinoma	RS	LR	8
Nair et al, 2000[90]	56	Percutaneous endoscopic gastrostomy in elderly patients with dementia	PS	LR	10
Scott et al, 2001[100]	9,016	Surgical patients receiving prophylactic antibiotic	RS	LR	29
Renal Dysfunction					
Lowrie and Lew, 1990[33]	19,746	Hemodialysis	RS	LR	17
USRDS, 1992[37]	3,399	Hemodialysis	RS	CR	37
Goldwasser et al, 1993[40]	184	New and long-standing hemodialysis patients	RS	CR	6
Owen et al, 1993[42]	13,473	Adult hemodialysis patients	RS	LR	8
Rocco et al, 1993[43]	45	CAPD	RS	LR	3
Collins et al, 1994[46]	1,773	First-time hemodialysis patients	RS	CR	6
Marcus et al, 1994[47]	89	Peritoneal dialysis	RS, PS	MR	3
Avram et al, 1995[48]	250	Hemodialysis	PS	CR	13
Lowrie et al, 1995[50]	17,926	Peritoneal dialysis and hemodialysis	RS	CR	36
Avram et al, 1996[52]	169	CAPD	PS	CR	9
Foley et al, 1996[53]	432	ESRD	MC, PS	CR	5
Iseki et al, 1996[55]	1,982	Chronic dialysis	RS	CR	18
Bologa et al, 1998[63]	90	Ambulatory adult hemodialysis patients	PS	CR	15
Chertow et al, 1998[64]	256	Acute renal failure	MC, PS	CR	22
Ifudu et al, 1998[68]	522	Hemodialysis patients ⩾ 20 y old	PS	CR	10
Leavey et al, 1998[70]	3,607	Hemodialysis	RS	CR	14
Noh et al, 1998[72]	106	CAPD	PS	CR	11
Owen et al, 1998[73]	18,144	Hemodialysis	RS	LR	5
Owen and Lowrie, 1998[74]	1,054	Hemodialysis	PS	LR	21
Obialo et al, 1999[79]	100	Acute renal failure	RS	LR	16
Ohashi et al, 1999[80]	91	CAPD	RS	CR	3
Zimmermann et al, 1999[82]	280	Stable hemodialysis patients	PS	CR	17
Chung et al, 2000[85]	213	CAPD	PS	CR	3
Moon et al, 2000[89]	32	Hemodialysis	RS	LR	3
Sharma et al, 2000[92]	41	CAPD	PS	CR	6
Tanna et al, 2000[93]	432	Peritoneal dialysis or hemodialysis	PS	CR	14
Yeun et al, 2000[94]	91	Hemodialysis	PS	CR	9
Cueto-Manzano et al, 2001[95]	627	CAPD	RS	CR	6
Gulati et al, 2001[96]	180	Children on continuous peritoneal dialysis	RS	LR	2
Kalantar-Zadeh et al, 2001[97]	83	Maintenance hemodialysis patients	PS	CR	17
Tokars et al, 2001[101]	796	Hemodialysis	MC, PS	CR	12
Tveit et al, 2001[102]	33,479	Renal transplant recipients	RS	LR	46
Bakewell et al, 2002[104]	88	Peritoneal dialysis	PS	MR	17
Klassen et al, 2002[105]	37,069	Maintenance hemodialysis	RS	CR	15
Sezer et al, 2002[107]	68	Hemodialysis	PS	CR	12
Stefoni et al, 2002[108]	155	ESRD patients on hemodialysis	PS	CR	7
Wong et al, 2002[110]	1,723	Pediatric patients with ESRD	RS	CR	8

surgery (OR 2.80; CI 2.18–3.58), and renal dysfunction (OR 2.48; CI 2.11–2.91) categories, respectively.

For the four categories of indications, the point estimates of OR were similar in magnitude and the pooled CI overlapped extensively. There was nevertheless evidence of significant overall statistical heterogeneity ($P < .005$), and additional possible contributors to heterogeneity (study design, patient age, multivariate analytic method, number of covariates, and study size) were investigated by sensitivity analysis (Table 2). There were no substantial between-stratum differences with respect to any of these variables, however, and hypoalbuminemia was significantly predictive of mortality in all strata. For instance, hypoalbuminemia was significantly associated with mortality both among retrospective and prospective cohort studies.

Thirteen included studies evaluated mortality but did not provide OR and CI estimates.[25,32,34,36,43–45,51,59,72,86,88,90] In eight of these studies, serum albumin was a significant

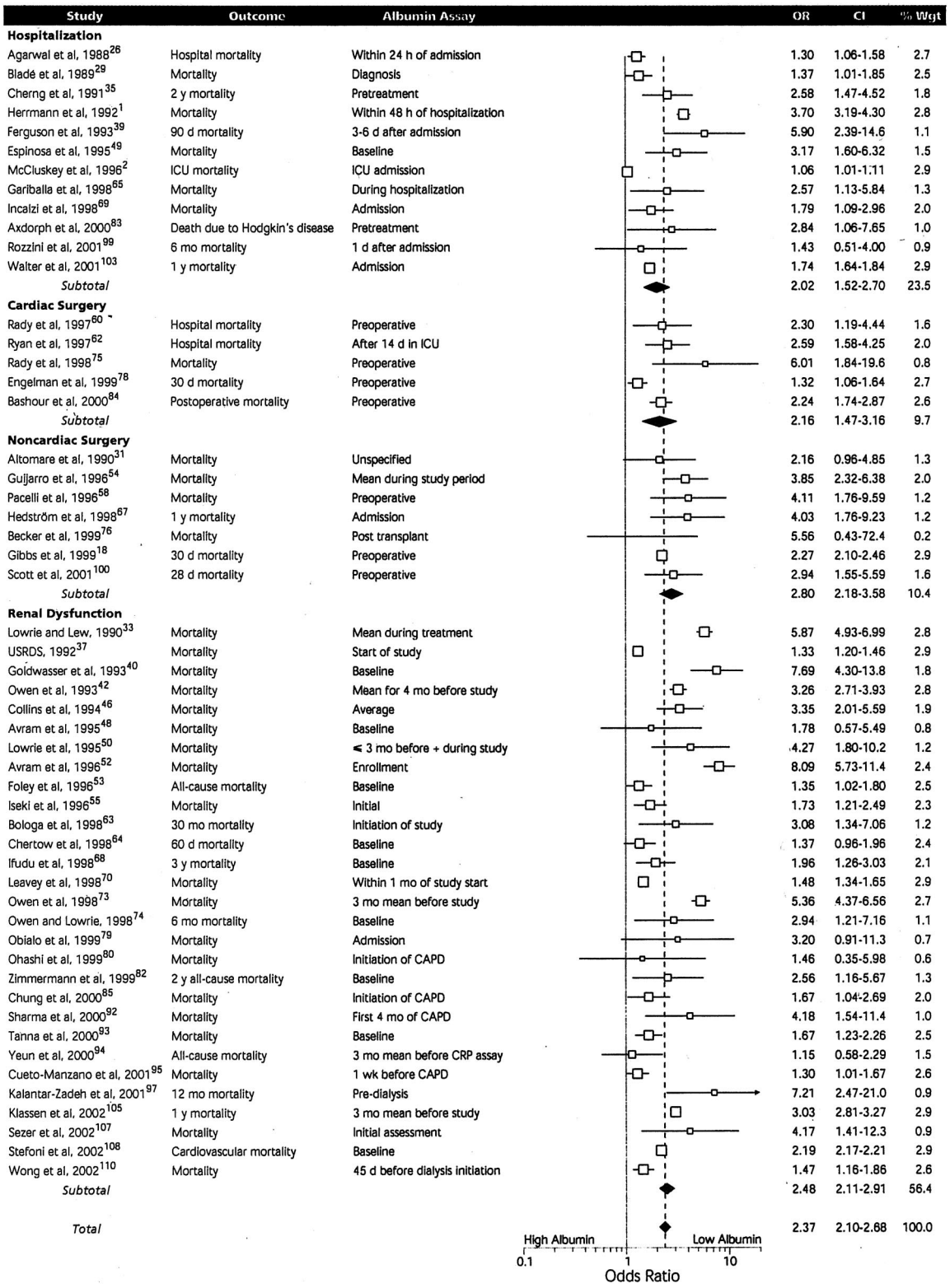

Figure 1. Effect of serum albumin on mortality. ICU, intensive care unit; CAPD, chronic ambulatory peritoneal dialysis; CRP, C-reactive protein.

independent predictor of mortality. Thus, the findings of these studies were qualitatively similar to those of the studies included in the meta-analysis shown in Figure 1.

To evaluate potential confounding by malnutrition, 15 included cohort studies[57,59,61,63,65,69,70,75,78,82,90,97,102,107,110] assessed body mass index as a covariate. For the 10 of these

Table 2. SENSITIVITY ANALYSES OF COHORT STUDIES

Study Attributes	Mortality			Morbidity		
	OR	CI	Studies	OR	CI	Studies
Retrospective	2.65	2.05–3.44	27	2.68	1.70–4.23	7
Prospective	2.05	1.82–2.32	26	1.72	1.42–2.09	11
Mean age < 60 y	2.63	2.00–3.46	24	1.69	1.33–2.14	8
Mean age ⩾ 60 y	2.24	1.92–2.62	29	1.94	1.57–2.41	10
Logistic regression	2.67	2.05–3.48	20	1.89	1.56–2.29	14
Cox regression	2.19	1.91–2.52	33	1.78	1.44–2.19	4
< 10 covariates evaluated	2.53	2.03–3.15	25	2.40	1.70–3.36	9
⩾ 10 covariates evaluated	2.27	1.91–2.69	28	1.66	1.34–2.05	9
< 1000 patients	2.34	1.92–2.86	34	2.11	1.55–2.88	9
⩾ 1000 patients	2.52	2.05–3.10	19	1.80	1.45–2.23	9
BMI evaluated as covariate	1.89	1.51–2.36	10	1.42	1.07–1.90	4
BMI not evaluated as covariate	2.43	2.12–2.78	43	1.98	1.69–2.33	14
CRP evaluated as covariate	2.77	1.66–4.62	6	—	—	—
CRP not evaluated as covariate	2.35	2.07–2.66	47	1.89	1.59–2.24	18

BMI, body mass index; CRP, C-reactive protein.

studies with a mortality endpoint and available OR and CI data (see Table 2), the pooled OR for mortality per 10-g/L serum albumin decrement was 1.89 (CI 1.51–2.36). The association between hypoalbuminemia and mortality was also shown to be independent of other nutritional indices such body weight, dry weight, body fat percentage, weight loss, cachexia, midarm circumference, and biceps and triceps skinfold thicknesses.[18,25,26,34,49,55,60,63,65,69,88,93,97,110]

In seven studies the effect of hypoalbuminemia on mortality was assessed with the inflammatory marker C-reactive protein (CRP) as a covariate.[72,74,82,83,94,97,107] For six of these studies OR estimates were available, and the pooled OR was 2.77 (CI 1.66–4.62), indicating that hypoalbuminemia remained a significant mortality predictor with the effects of CRP taken into account (see Table 2). The significant association between hypoalbuminemia and mortality also persisted when other markers of inflammation were evaluated as covariates (white blood cell count, lymphocyte count, neutrophil count, interleukin-6, interleukin-10, tumor necrosis factor-α, β2-microglobulin, serum amyloid A, transferrin, and fibrinogen).[25,26,29,32,34,44,49,50,58,63,65,69,74,82,83,95,97]

Morbidity

Hypoalbuminemia was also an independent predictor of morbidity across all studies and within each of the four categories of clinical indications (Fig. 2). Morbidity was reported as overall morbidity or as one or more types of individual complications, most frequently involving cardiovascular morbidity, infection, or organ dysfunction. Thus, morbidity did not constitute a single homogeneous outcome measure across studies, and the seriousness of particular complications evaluated was not necessarily similar.

The pooled OR for morbidity among all 18 studies assessing this endpoint was 1.89 (CI 1.59–2.24), indicating a statistically significant 89% increase in odds of complications corresponding to a 10-g/L reduction in serum albumin. Significant increases in morbidity odds of 178%, 52%, 73%, and 102% were documented respectively among the subsets of studies involving hospitalization (OR 2.78; CI 1.30–5.98), cardiac surgery (OR 1.52; CI 1.12–2.04), noncardiac surgery (OR 1.73; CI 1.67–1.79), and renal dysfunction (OR 2.02; CI 1.48–2.74).

There was significant statistical heterogeneity with respect to the morbidity endpoint ($P < .005$). In sensitivity analyses between-stratum pooled estimates of OR did not differ notably, and CI overlapped extensively (see Table 2). Significantly increased morbidity odds per 10-g/L serum albumin decrement were apparent for all subsets of trials with data represented in Table 2.

Morbidity was addressed in eight studies that could not be included in the meta-analysis of Figure 2 due to unavailability of OR and CI data.[24,25,27,28,30,34,56,88] In seven of these studies serum albumin was found to be a significant independent predictor of morbidity.

In four studies with an OR estimate provided for morbidity and inclusion of body mass index as a covariate (see Table 2), hypoalbuminemia was significantly associated with morbidity (OR 1.42; CI 1.07–1.90). Hypoalbuminemia also remained a significant independent morbidity predictor in studies taking into account markers of nutritional status other than body mass index such as body weight, body surface area, degree of weight loss, rate of weight loss, triceps skinfold, midarm muscle circumference, and cachexia.[18,24,25,34,60,61,102] While none of the included studies assessed morbidity with CRP as a covariate, in three studies hypoalbuminemia was associated with significantly increased morbidity when other markers of inflammation were taken into account

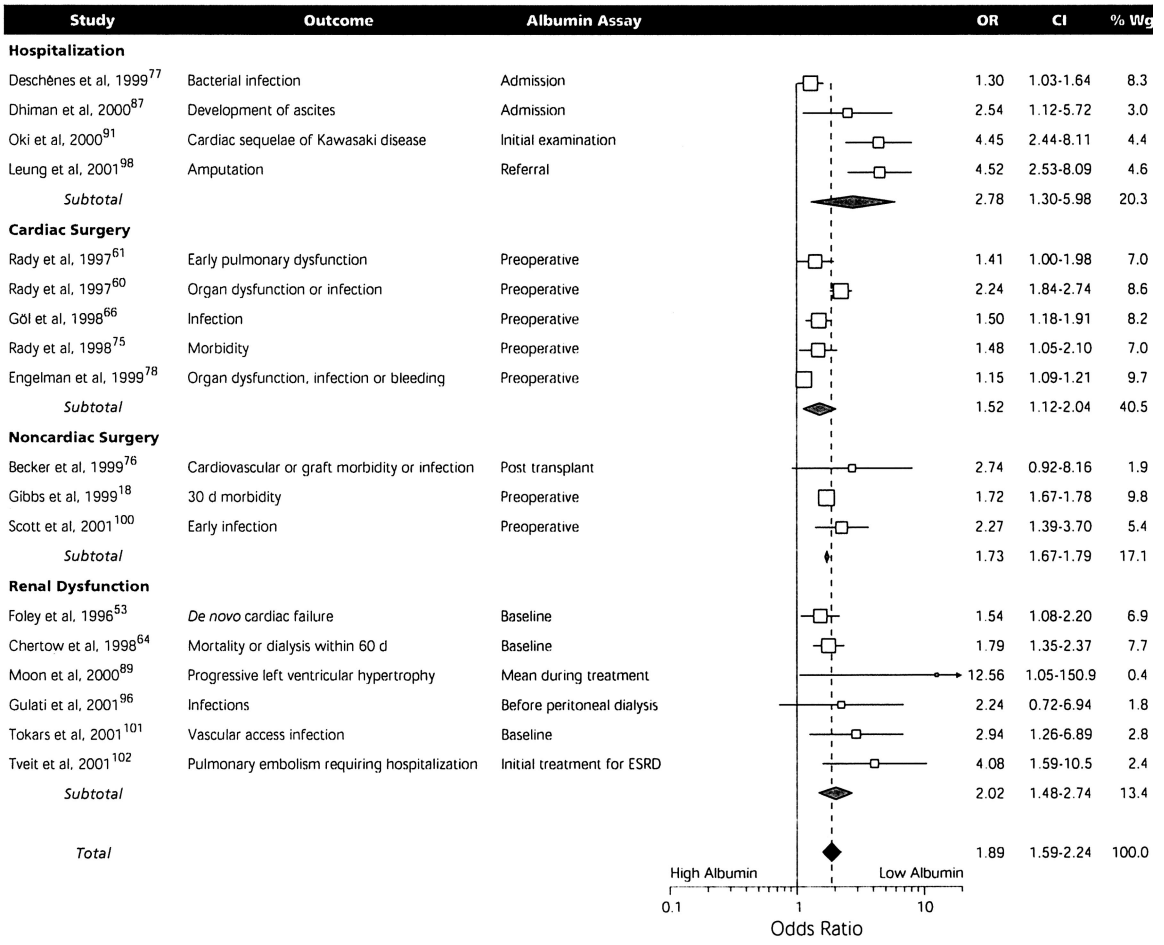

Figure 2. Effect of serum albumin on morbidity. ESRD, end-stage renal disease.

(white blood cell count, total lymphocyte count, and serum transferrin).[24,25,27]

Length of Stay

Hypoalbuminemia was a significant independent predictor of prolongation in both ICU and hospital stay. Length of ICU stay was a subject of three included studies.[60,78,84] The pooled OR for ICU stay was 1.28 (CI 1.16–1.40), indicating a significant 28% increase in odds for prolonged ICU stay per 10-g/L decrement in serum albumin.

OR and CI estimates for prolonged hospital stay were available from four included studies.[1,39,60,78] The corresponding pooled OR was 1.71 (CI 1.33–2.21), revealing a significant hypoalbuminemia-related increase of 71% in odds of prolonged hospital stay. In five additional included studies,[30,38,41,47,71] length of hospital stay was evaluated, but OR and CI estimates were unavailable. Serum albumin was a significant independent predictor of prolonged hospital stay in all five studies.

Resource Utilization

In nine studies resource utilization was evaluated with respect to ventilatory support,[60,78,81,106] postoperative transfusion,[57] and hospitalization (i.e., admission or readmission to hospital).[43,76,96,97] The economic impact of each type of resource utilization was not quantified in the study reports and cannot be presumed to be similar in magnitude.

Among the eight studies supplying OR data, hypoalbuminemia significantly increased resource utilization by 66% per 10-g/L serum albumin decline (OR 1.66; CI 1.17–2.36). In the ninth study, no OR estimate was available, but hypoalbuminemia was significantly associated with increased resource utilization.

Other Endpoints

In two trials on the relation of hypoalbuminemia to treatment failure,[95,96] the pooled OR was 2.07 (CI 0.52–8.30). In one study hypoalbuminemia was predictive of significantly poorer quality of life.[104] The odds of overcoagulation were increased in hypoalbuminemic patients with venous thromboembolism (OR 3.60; CI 1.32–9.77).[109]

Controlled Trials

Nine prospective controlled trials with 535 total patients conformed to all inclusion criteria.[111–119] The median num-

Table 3. CHARACTERISTICS OF CONTROLLED TRIALS DESIGNED TO EVALUATE CORRECTION OF HYPOALBUMINEMIA

Trial	Clinical Setting	Test Regimen	Endpoints	Complication Types Reported
McMurray et al, 1948[111]	Low birth weight premature infants	1–2 injections per week of 3 cc 25 g/dL albumin per pound body weight vs no albumin	Serum albumin; weight gain, hospital stay, morbidity, mortality	Gastroenteritis; jaundice
Smith et al, 1950[112]	Low birth weight premature infants	25% salt-poor albumin 0.5–0.75 g per pound body weight twice weekly	Serum albumin; morbidity, mortality	Pneumonia, diarrhea, edema, distension, vomiting
Ford et al, 1987[113]	Hypoalbuminemia (serum albumin < 30 g/L) in pediatric patients selected for enteral tube feeding via stomach or small bowel	Salt poor albumin according to formula ((3.5 g/dL − serum albumin (g/dL)) × (weight (kg) × 3) over 2–3 d in divided doses vs no albumin	Tolerance to enteral feeding; serum albumin	Enteral feeding intolerance; sepsis; persistent diarrhea; aspiration or tube-related complications
Brown et al, 1988[114]	Hypoalbuminemia (serum albumin < 30 g/L) in adult patients requiring TPN because of general surgery, multiple trauma or medical conditions	12.5 g/L albumin, then 25–37.5 g/d albumin vs no albumin	Hospital morbidity	Septicemia; intra-abdominal abscess; fistula; urinary tract infection; pneumonia; wound infection; wound dehiscence; congestive heart failure; phlebitis; respiratory failure; pulmonary embolus; cerebrovascular accident; septic shock
Foley et al, 1990[115]	Hypoalbuminemia (serum albumin < 25 g/L) in critically ill adult patients referred for TPN	25–50 g/d 25% albumin vs no albumin	Mortality; major complication rate	Major arrhythmia; myocardial infarction; deep vein thrombosis; shock; stroke; pneumonia; pneumothorax; respiratory failure; cholecystitis; bleeding; small-bowel obstruction; acute renal failure; bacterial sepsis; viral sepsis; fungal sepsis; intra-abdominal sepsis; mediastinitis; *Clostridium difficile* enterocolitis; line sepsis; diffuse peritonitis; urinary tract infection; enterocutaneous fistula; decubitus ulcer; wound infection
Kanarek et al, 1992[116]	Sick newborn infants with respiratory distress, hypotension, hypoalbuminemia (serum albumin < 30 g/L) and a requirement for TPN	Albumin to maintain 30 g/L serum albumin vs no added albumin	Serum albumin; severity of respiratory distress; mean arterial blood pressure; weight gain; incidence of complications	Bronchopulmonary dysplasia; necrotizing enterocolitis
Wojtysiak et al, 1992[117]	Hypoalbuminemia (serum albumin < 30 g/L) in adult patients requiring TPN resulting from multiple trauma, general surgery, carcinoma or medical conditions	Albumin 25 g/L as a continuous infusion for a 5 d study period vs no albumin	Serum albumin; COP; free water clearance; electrolyte-free water resorption; sodium excretion	Bacteremia; pneumonia; urinary tract infection; intraabdominal sepsis; wound infection; vaginal infection; cholangitis

(*continues*)

TPN, total parenteral nutrition; COP, colloid osmotic pressure.

Table 3 *(continued).*

Trial	Clinical Setting	Test Regimen	Endpoints	Complication Types Reported
Golub et al, 1994[118]	Hypoalbuminemia (serum albumin < 30 g/L) upon admission of adult patients to surgical intensive care unit due to vascular insufficiency, hip fracture, gastrointestinal bleeding, cancer, perforated viscus, pancreatitis, intra-abdominal infection or bowel obstruction; all patients received nutritional support in the form of a diet, TPN or enteral feedings	50 mL of 25% albumin every 8 h to maintain serum albumin > 30 g/L vs no albumin	Morbidity; mortality	Pneumonia; sepsis; wound infection; urinary tract infection; line infection; abdominal sepsis; respiratory failure; congestive heart failure; dehiscence; decubitus ulcer; liver failure; myocardial infarction; arrhythmia; gastrointestinal bleeding; renal failure; cardiac arrest; cerebrovascular accident; enteral feeding intolerance
Rubin et al, 1997[119]	Hypoalbuminemia (< 25 g/L serum albumin) in adult patients receiving TPN	25 g/d albumin vs 100 mL/d normal saline	Morbidity; mortality; serum albumin	Bacteremia; pneumonia

ber of patients per trial was 38 (range 24–219). Seven of the trials were randomized.[111,114–119] None was unpublished. Characteristics of the included controlled trials are summarized in Table 3.

Four trials involved pediatric patients.[111–113,116] For the adult studies the median patient age was 59 years (range 47–71). The median duration of follow-up for both adult and pediatric trials was 26 days (range 5–150).

Three trials involved some form of blinding.[114,116,119] The method of allocation concealment was adequate in four of six randomized trials,[114,116,118,119] unclear in two,[115,117] and inadequate in one.[111] Morbidity was an endpoint of all included trials except one.[117] In four trials individual control-group patients crossed over to albumin therapy.[114,115,117,118] The median number of patients crossing over was 2.5 (range 2–6).

Pooled Morbidity

As shown in Figure 3, the pooled OR for occurrence of one or more complications in individual patients was 0.74 (CI 0.36–1.49). Thus, morbidity was lower among albumin recipients, but the effect was not statistically significant. The pooled odds ratio was similar after exclusion of the two nonrandomized trials (OR 0.81; CI 0.41–1.60).[112,113] There was no evidence of publication bias ($P = .367$). Among all control group patients, 48% (125/262) experienced one or more complications.

Dose Dependency

Significant between-trial heterogeneity was apparent with respect to the OR for complications ($P = .006$), and possible sources of heterogeneity such as year of publication, duration of follow-up, and albumin dose as reflected by attained serum albumin level during therapy were investigated by meta-analysis regression. The OR for complications was not significantly related to either the year of publication ($P = .622$) or duration of follow-up ($P = .220$).

Pooled baseline serum albumin concentration did not differ significantly ($P = .79$) between the albumin (24.4 ± 1.4 g/L) and control group (24.5 ± 1.4 g/L). Attained serum albumin level during therapy was reported in eight of nine trials. As shown in Figure 4,[120] the OR for complications declined progressively as attained serum albumin level increased ($P = .002$). In the five studies with an attained albumin level of more than 30 g/L, complications were less frequent in albumin recipients than control-group patients and vice versa in the three studies with an attained albumin level of less than 30 g/L. The between-study variance determined by method-of-moments estimator was 0.0815 in the meta-analysis regression as contrasted with 0.656 with no account taken of attained serum albumin level. Thus, the dose effect could explain 88% of total between-study variance. The significant observed dose-response relationship also persisted after exclusion of two early trials ($P = .026$).[111,112] Meta-analysis regression failed to reveal any significant relationship between morbidity and baseline se-

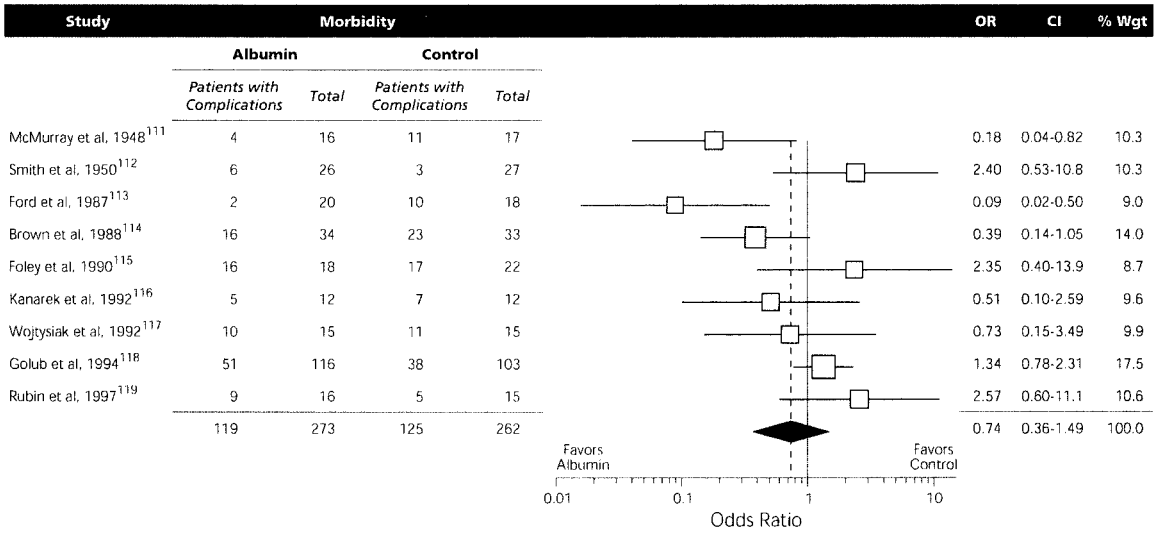

Figure 3. Morbidity in controlled trials evaluating the correction of hypoalbuminemia.

rum albumin of either the albumin group ($P = .22$) or the control group ($P = .33$) or the weighted average of baseline serum albumin in both groups ($P = .27$).

DISCUSSION

Our meta-analysis is the first to assemble comprehensive evidence—based largely on recently reported data analyzed by multivariate methods—that addresses the long-standing debate over the clinical importance of hypoalbuminemia in the acutely ill. It also provides a novel quantitative model of dose dependency that may explain the disparate results obtained thus far in trials on the correction of hypoalbuminemia.

We found hypoalbuminemia to be a powerful, reproducible, dose-dependent, independent risk factor for poor outcome in the acutely ill. This association was striking both for its consistency and pervasiveness. Unfavorable sequelae associated with lower serum albumin were evident in hospitalized patients generally and in populations undergoing cardiac and noncardiac surgery or suffering from renal dysfunction. The hypoalbuminemia effect manifested itself across the full spectrum of clinical outcomes: mortality, morbidity, length of both ICU and hospital stay, and increased resource utilization. However, the evidence on length of stay, resource utilization, and certain other endpoints was substantially more limited than that on mortality and morbidity.

Because of the strength of the association and low cost of serum albumin assays, monitoring albumin levels has been advocated as a prognostic tool to identify higher-risk patients.[1,18,78] As vividly demonstrated in the largest included

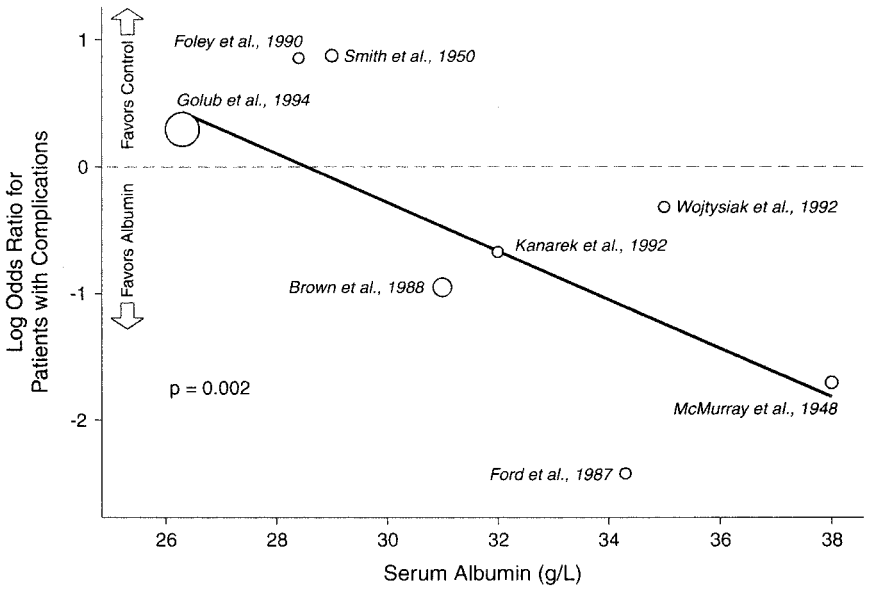

Figure 4. Meta-analysis regression assessing the effect of attained serum albumin level on morbidity in controlled trials to evaluate the correction of hypoalbuminemia. Data points are scaled in proportion to precision. Incidence of complications was reported on a per-patient basis in six trials.[111–115,118] The average number of complications per patient in these trials was 1.1. For the other three studies complications per patient were estimated from total complication data using 1.1 as the conversion factor. For analytic purposes the attained serum albumin reported in two early trials[111,112] was adjusted downward by 13 g/L, corresponding to the difference between the mean serum albumin for healthy term infants using contemporary assay methods (35 g/L)[120] and the corresponding mean using older methodology (48 g/L), as documented in one of the two early trials.[111]

cohort study, involving 54,215 noncardiac surgery patients,[18] both mortality and morbidity continuously increased as serum albumin progressively decreased over the entire range of albumin levels between 22 and 46 g/L, and there was no evidence of any threshold above which albumin no longer substantially affected these outcomes. In light of these findings, clinical risk stratification strategies emphasizing only severe hypoalbuminemia (e.g., serum albumin < 25 g/L) may insufficiently recognize the increased risk of patients with higher albumin levels (e.g., 25–35 g/L).

Several limitations of our meta-analysis should be recognized. Reliance on multivariate analysis of cohort study results was a principal feature of the meta-analysis, and the included studies addressed a broad array of variables. Nevertheless, unidentified confounding variables may exist, and the possibility cannot be dismissed that the hypoalbuminemia effect is merely an epiphenomenon indicative of other pathologic processes, as has often been argued. Furthermore, among the included cohort studies both the numbers and types of covariates differed widely. Additionally, quantitative and qualitative differences were apparent among the complications assessed in both the included cohort studies and controlled trials. Because of these differences in the number, type and seriousness of complications quantitatively combined, the morbidity endpoint evaluated in our meta-analysis may with some justification be regarded as heterogeneous from a clinical point of view.

Our data indicate that two important potential confounding variables—malnutrition and inflammation—cannot fully explain the hypoalbuminemia effect. The malnourished state has long been recognized as a potential precipitating factor in the development of hypoalbuminemia. We found that the significant association between hypoalbuminemia and poor outcome persisted after adjustment for body mass index and other measures of nutritional status.

Growing attention has centered on the role of inflammatory processes in inducing hypoalbuminemia. By increasing vascular permeability, inflammatory mediators may promote escape of albumin into the extravascular space. Such mediators may also reprioritize hepatic protein synthesis in favor of acute phase reactants at the expense of albumin production. CRP, an acute phase protein produced by the liver, is one marker of inflammation that has been proposed to account for the association between hypoalbuminemia and poor outcome.[94] Nevertheless, we found the effects of hypoalbuminemia on outcome to be independent of CRP, as well as other markers of inflammation. Such observations make plain that inflammation, at least as manifested by altered levels of currently identified inflammatory markers, may contribute to reduced serum albumin levels but nevertheless cannot fully account for the association between hypoalbuminemia and poor outcome. It is possible, however, that other as yet undetectable derangements in patient inflammatory response might more completely explain the hypoalbuminemia effect.

Hypoalbuminemia may be causally related to poor outcome. A previous systematic review addressed the association between serum albumin and mortality in 10 cohort studies with multivariate analysis involving 55,965 healthy subjects and acutely ill patients.[7] In that review, circulating albumin concentration was inversely related to mortality risk in a progressive fashion over its entire range. The association persisted after adjustment for other known risk factors and pre-existing illness and exclusion of early mortality, and plausible biologic mechanisms underlying the effect were noted. The review prompted the conclusion that albumin may exert a direct protective effect. Our review, focusing exclusively on the acutely ill and addressing a wider range of outcomes, also supports this conclusion.

Several mechanisms might help explain the apparent protective effects of serum albumin. Clearly, serum albumin plays diverse, complex, and important roles in maintaining physiologic homeostasis. At reduced albumin levels these homeostatic functions may be impaired, resulting in the development and/or progression of pathologic processes underlying poor outcome. The full spectrum of albumin biologic actions has as yet not been fully delineated and forms the center of an active field of recent research. Nevertheless, a number of its actions are well established, such as the ability to maintain normal colloid osmotic pressure (COP). Reduction in COP promotes edema formation. While many patients may tolerate edema adequately, others may be adversely affected, particularly by pulmonary, myocardial, or intestinal edema.

The ability of serum albumin to sustain COP may only be one of many possible protective effects of albumin. In a study of 145 patients with prolonged critical illness, hypoalbuminemia was associated with increased mortality, even though in these patients COP had been maintained by administration of artificial colloid.[121] Therefore, the hypoalbuminemia effect might be at least partly reliant on the additional properties of albumin such as its antioxidant and free radical-scavenging activity, capacity to prevent apoptosis, and affinity for binding lipids, drugs, toxic substances, and other ligands.[122–124] The antioxidant effects of albumin, for example, may translate into biologic protection of potential clinical relevance. Albumin decreased both hydrogen peroxide formation and reperfusion injury in isolated rat hearts.[125] It also prevented ischemic and hypoxic damage in isolated perfused rat livers.[126] Albumin inhibited peroxidation of erythrocyte membrane lipids in chronic hemodialysis patients.[127] Bilirubin bound to albumin substantially prolonged the survival of human ventricular heart muscle cells exposed to oxyradicals generated in situ.[128]

Because of its high frequency in a broad range of pathologic conditions, hypoalbuminemia might plausibly be interpreted as a normal compensatory mechanism not requiring intervention. For instance, albumin redistribution into the interstitial space might provide protection from oxidative stress affecting extravascular tissues during disease states. Nonetheless, hypoalbuminemia-related reductions in COP, intravascular antioxidative reserve, binding activity,

and other protective effects of albumin in the plasma compartment are difficult to view as a beneficial adaptation.

If indeed serum albumin exerts a net protective effect, then exogenous albumin therapy might benefit hypoalbuminemic patients. Furthermore, even if albumin level did primarily reflect other upstream pathologic processes, albumin therapy might nevertheless be effective as a downstream intervention to interrupt the chain of events culminating in poor outcome. Administration of purified albumin is clearly effective in raising serum albumin levels.[114–116,118,129] Even in sepsis, a condition marked by increased vascular permeability, administered albumin can produce a prompt and sustained rise in serum albumin concentration.[130]

Available evidence from controlled trials is, however, inconclusive as to the potential benefits to be derived from correcting hypoalbuminemia. In our meta-analysis, no significant overall reduction in morbidity was demonstrable. Nonetheless, the existing controlled trial evidence is limited. Furthermore, based on our meta-analysis regression, attained serum albumin level appears to be a major determinant of morbidity. Thus, the attained albumin level accounted for most of the between-study variance, indicating that the differences in morbidity results reported among the included controlled trials were predominantly due to dose effects. This analysis suggests the hypothesis that administering sufficient exogenous albumin to achieve a serum albumin level of more than 30 g/L might lessen morbidity in hypoalbuminemic patients. The significant within-study findings for the trials in our meta-analysis regression are consistent with this hypothesis.

In the three studies with an attained serum albumin level of less than 30 g/L, no within-study evidence was obtained of clinical benefit due to albumin therapy.[112,115,118] Conversely, such benefit was demonstrable in the four studies with a morbidity endpoint and an attained albumin level of more than 30 g/L. Specifically, in these studies with higher attained albumin levels, the albumin group experienced an acceleration of time to regain birthweight and fewer illnesses;[111] improved nutritional status and tolerance to enteral feeding;[113] fewer total hospital complications and lower frequencies of septicemia and pneumonia;[114] and greater relief of hypotension and shorter time to regain birthweight.[116]

A morbidity benefit due to albumin therapy, if demonstrable, might improve the overall costs of care. Significant edema may limit mobilization and delay convalescence. In one included cohort study of 9,352 cardiac surgery patients,[66] hypoalbuminemia was predictive of postoperative infection, and ICU stay was increased over fivefold in patients developing infections (13.4 $\pm$ 20.1 days vs. 2.5 $\pm$ 3.8 days, $P < .001$). In another included cohort study of elderly hospitalized patients, hypoalbuminemia was associated with increased risk for a discharge diagnosis of delirium.[27] Patients with this diagnosis incurred average total hospital charges of $17,377 versus $11,946 for those without the diagnosis. Mean hospital stay was 23.7 days for patients with delirium compared with 13.6 days for nondelirious patients. Savings resulting from a reduced morbidity rate might exceed the acquisition cost of albumin.

Further well-designed, adequately powered controlled clinical trials are needed to resolve the question whether correcting hypoalbuminemia is beneficial. Pending the results of such future studies, there does appear to be a coherent rationale for albumin replacement therapy and no compelling basis to withhold albumin if it is deemed clinically appropriate in hypoalbuminemic patients.

References

1. Herrmann FR, Safran C, Levkoff SE, et al. Serum albumin level on admission as a predictor of death, length of stay, and readmission. *Arch Intern Med.* 1992;152:125–130.
2. McCluskey A, Thomas AN, Bowles BJ, et al. The prognostic value of serial measurements of serum albumin concentration in patients admitted to an intensive care unit. *Anaesthesia.* 1996;51:724–727.
3. Reinhardt GF, Myscofski JW, Wilkens DB, et al. Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. *JPEN J Parenter Enteral Nutr.* 1980;4:357–359.
4. Margarson MP, Soni N. Serum albumin: touchstone or totem? *Anaesthesia.* 1998;53:789–803.
5. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest.* 1991;100:1619–1636.
6. Vermeulen LC, Jr, Ratko TA, Erstad BL, et al. A paradigm for consensus. The University Hospital Consortium guidelines for the use of albumin, nonprotein colloid, and crystalloid solutions. *Arch Intern Med.* 1995;155:373–379.
7. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. *J Clin Epidemiol.* 1997;50:693–703.
8. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2001;135:149–164.
9. Alderson P, Bunn F, Lefebvre C, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev.* 2002;1:CD001208.
10. Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. *N Engl J Med.* 2002;346:1061–1066.
11. Gøtzsche PC. Why we need a broad perspective on meta-analysis. It may be crucially important for patients. *Br Med J.* 2000;321:585–586.
12. Abbott RD. Logistic regression in survival analysis. *Am J Epidemiol.* 1985;121:465–471.
13. Ingram DD, Kleinman JC. Empirical comparisons of proportional hazards and logistic regression models. *Stat Med.* 1989;8:525–538.
14. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev.* 1987;9:1–30.
15. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol.* 1992;135:1301–1309.
16. Sharp S, Sterne J. Meta-analysis. *Stata Tech Bull.* 1997;STB-38:100–106.
17. Bradburn MJ, Deeks JJ, Altman DG. metan—an alternative meta-analysis command. *Stata Tech Bull.* 1998;STB-44:86–100.
18. Gibbs J, Cull W, Henderson W, et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg.* 1999;134:36–42.
19. Jüni P, Witschi A, Bloch R, et al. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999; 282:1054–1060.

20. Sharp S. Meta-analysis regression. *Stata Tech Bull.* 1998;STB-42: 148–155.
21. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *Br Med J.* 1997;315:629–634.
22. Steichen TJ. Tests for publication bias in meta-analysis. *Stata Tech Bull.* 1998;STB-41:125–133.
23. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* 1995;273:408–412.
24. Buzby GP, Mullen JL, Matthews DC, et al. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg.* 1980;139:160–167.
25. Harvey KB, Moldawer LL, Bistrian BR, et al. Biological measures for the formulation of a hospital prognostic index. *Am J Clin Nutr.* 1981;34:2013–2022.
26. Agarwal N, Acevedo F, Leighton LS, et al. Predictive ability of various nutritional variables for mortality in elderly people. *Am J Clin Nutr* 1988;48:1173–1178.
27. Levkoff SE, Safran C, Cleary PD, et al. Identification of factors associated with the diagnosis of delirium in elderly hospitalized patients. *J Am Geriatr Soc.* 1988;36:1099–1104.
28. Trzepacz PT, Brenner RP, Coffman G, et al. Delirium in liver transplantation candidates: discriminant analysis of multiple test variables. *Biol Psychiatry.* 1988;24:3–14.
29. Bladé J, Rozman C, Cervantes F, et al. A new prognostic system for multiple myeloma based on easily available parameters. *Br J Haematol.* 1989;72:507–511.
30. Rich MW, Keller AJ, Schechtman KB, et al. Increased complications and prolonged hospital stay in elderly cardiac surgical patients with low serum albumin. *Am J Cardiol.* 1989;63:714–718.
31. Altomare DF, Serio G, Pannarale OC, et al. Prediction of mortality by logistic regression analysis in patients with postoperative enterocutaneous fistulae. *Br J Surg.* 1990;77:450–453.
32. Lai EC, Tam PC, Paterson IA, et al. Emergency surgery for severe acute cholangitis. The high-risk patients. *Ann Surg.* 1990;211:55–59.
33. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis.* 1990;15: 458–482.
34. Sullivan DH, Patch GA, Walls RC, et al. Impact of nutrition status on morbidity and mortality in a select population of geriatric rehabilitation patients. *Am J Clin Nutr.* 1990;51:749–758.
35. Cherng NC, Asal NR, Kuebler JP, et al. Prognostic factors in multiple myeloma. *Cancer.* 1991; 67:3150–3156.
36. Levis A, Ficara F, Marmont F, et al. Prognostic significance of serum albumin in chronic lymphocytic leukemia. *Haematologica.* 1991;76: 113–119.
37. United States Renal Data System. Comorbid conditions and correlations with mortality risk among 3,399 incident hemodialysis patients. *Am J Kidney Dis.* 1992;20:32–38.
38. Burr RG, Clift-Peace L, Nuseibeh I. Haemoglobin and albumin as predictors of length of stay of spinal injured patients in a rehabilitation centre. *Paraplegia.* 1993;31:473–478.
39. Ferguson RP, O'Connor P, Crabtree B, et al. Serum albumin and prealbumin as predictors of clinical outcomes of hospitalized elderly nursing home residents. *J Am Geriatr Soc.* 1993;41:545–549.
40. Goldwasser P, Mittman N, Antignani A, et al. Predictors of mortality in hemodialysis patients. *J Am Soc Nephrol.* 1993;3:1613–1622.
41. McEllistrum MC, Collins JC, Powers JS. Admission serum albumin level as a predictor of outcome among geriatric patients. *South Med J.* 1993;86:1360–1361.
42. Owen WF, Jr, Lew NL, Liu Y, et al. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med.* 1993;329:1001–1006.
43. Rocco MV, Jordan JR, Burkart JM. The efficacy number as a predictor of morbidity and mortality in peritoneal dialysis patients. *J Am Soc Nephrol.* 1993;4:1184–1191.
44. Sirott MN, Bajorin DF, Wong GY, et al. Prognostic factors in patients with metastatic malignant melanoma. A multivariate analysis. *Cancer.* 1993;72:3091–3098.
45. Toledo C, Salmerón JM, Rimola A, et al. Spontaneous bacterial peritonitis in cirrhosis: predictive factors of infection resolution and survival in patients treated with cefotaxime. *Hepatology.* 1993;17: 251–257.
46. Collins AJ, Ma JZ, Umen A, et al. Urea index and other predictors of hemodialysis patient survival. *Am J Kidney Dis.* 1994;23:272–282.
47. Marcus RG, Chaing E, Dimaano F, et al. Serum albumin: associations and significance in peritoneal dialysis. *Adv Perit Dial.* 1994;10:94–98.
48. Avram MM, Mittman N, Bonomini L, et al. Markers for survival in dialysis: a seven-year prospective study. *Am J Kidney Dis.* 1995; 26:209–219.
49. Espinosa E, Feliu J, Zamora P, et al. Serum albumin and other prognostic factors related to response and survival in patients with advanced non-small cell lung cancer. *Lung Cancer.* 1995;12:67–76.
50. Lowrie EG, Huang WH, Lew NL. Death risk predictors among peritoneal dialysis and hemodialysis patients: a preliminary comparison. *Am J Kidney Dis.* 1995;26:220–228.
51. Violi F, Ferro D, Basili S, et al. Prognostic value of clotting and fibrinolytic systems in a follow-up of 165 liver cirrhotic patients. CALC Group. *Hepatology.* 1995;22:96–100.
52. Avram MM, Fein PA, Bonomini L, et al. Predictors of survival in continuous ambulatory peritoneal dialysis patients: a five-year prospective study. *Perit Dial Int.* 1996;16:S190–194.
53. Foley RN, Parfrey PS, Harnett JD, et al. Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol.* 1996;7:728–736.
54. Guijarro C, Massy ZA, Wiederkehr MR, et al. Serum albumin and mortality after renal transplantation. *Am J Kidney Dis.* 1996;27:117–123.
55. Iseki K, Uehara H, Nishime K, et al. Impact of the initial levels of laboratory variables on survival in chronic dialysis patients. *Am J Kidney Dis.* 1996;28:541–548.
56. Magovern JA, Sakert T, Magovern GJ, et al. A model that predicts morbidity and mortality after coronary artery bypass graft surgery. *J Am Coll Cardiol.* 1996;28:1147–1153.
57. Magovern JA, Sakert T, Benckart DH, et al. A model for predicting transfusion after coronary artery bypass grafting. *Ann Thorac Surg.* 1996;61:27–32.
58. Pacelli F, Doglietto GB, Alfieri S, et al. Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. *Arch Surg.* 1996; 131:641–645.
59. Friedenberg F, Jensen G, Gujral N, et al. Serum albumin is predictive of 30-day survival after percutaneous endoscopic gastrostomy. *JPEN J Parenter Enteral Nutr.* 1997;21:72–74.
60. Rady MY, Ryan T, Starr NJ. Clinical characteristics of preoperative hypoalbuminemia predict outcome of cardiovascular surgery. *JPEN J Parenter Enteral Nutr.* 1997;21:81–90.
61. Rady MY, Ryan T, Starr NJ. Early onset of acute pulmonary dysfunction after cardiovascular surgery: risk factors and clinical outcome. *Crit Care Med* 1997;25:1831–1839.
62. Ryan TA, Rady MY, Bashour CA, et al. Predictors of outcome in cardiac surgical patients with prolonged intensive care stay. *Chest* 1997;112:1035–1042.
63. Bologa RM, Levine DM, Parker TS, et al. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. *Am J Kidney Dis.* 1998;32:107–114.
64. Chertow GM, Lazarus JM, Paganini EP, et al. Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal Failure Study Group. *J Am Soc Nephrol* 1998;9:692–698.
65. Gariballa SE, Parker SG, Taub N, et al. Influence of nutritional status on clinical outcome after acute stroke. *Am J Clin Nutr.* 1998;68:275–281.

66. Göl MK, Karahan M, Ulus AT, et al. Bloodstream, respiratory, and deep surgical wound infections after open heart surgery. *J Card Surg.* 1998;13:252–259.
67. Hedström M, Gröndal L, Örtquist A, et al. Serum albumin and deep infection in femoral neck fractures. A study of 437 cases followed for one year. *Int Orthop.* 1998;22:182–184.
68. Ifudu O, Paul HR, Homel P, et al. Predictive value of functional status for mortality in patients on maintenance hemodialysis. *Am J Nephrol.* 1998;18:109–116.
69. Incalzi R, Capparella O, Gemma A, et al. Inadequate caloric intake: a risk factor for mortality of geriatric patients in the acute-care hospital. *Age Ageing.* 1998;27:303–310.
70. Leavey SF, Strawderman RL, Jones CA, et al. Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. *Am J Kidney Dis.* 1998;31:997–1006.
71. Marinella MA, Markert RJ. Admission serum albumin level and length of hospitalization in elderly patients. *South Med J.* 1998;91: 851–854.
72. Noh H, Lee SW, Kang SW, et al. Serum C-reactive protein: a predictor of mortality in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int.* 1998;18:387–394.
73. Owen WF Jr, Chertow GM, Lazarus JM, et al. Dose of hemodialysis and survival: differences by race and sex. *JAMA* 1998;280:1764–1768.
74. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int.* 1998;54:627–636.
75. Rady MY, Ryan T, Starr NJ. Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. *Crit Care Med.* 1998;26:225–235.
76. Becker BN, Becker YT, Heisey DM, et al. The impact of hypoalbuminemia in kidney-pancreas transplant recipients. *Transplantation.* 1999;68:72–75.
77. Deschènes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. *Am J Gastroenterol.* 1999;94:2193–2197.
78. Engelman DT, Adams DH, Byrne JG, et al. Impact of body mass index and albumin on morbidity and mortality after cardiac surgery. *J Thorac Cardiovasc Surg.* 1999;118:866–873.
79. Obialo CI, Okonofua EC, Nzerue MC, et al. Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure. *Kidney Int.* 1999;56:1058–1063.
80. Ohashi H, Oda H, Ohno M, et al. Predictors of survival in continuous ambulatory peritoneal dialysis patients: the importance of left ventricular hypertrophy and diabetic nephropathy. *Adv Perit Dial.* 1999; 15:87–90.
81. Rady MY, Ryan T. Perioperative predictors of extubation failure and the effect on clinical outcome after cardiac surgery. *Crit Care Med.* 1999;27:340–347.
82. Zimmermann J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int.* 1999;55:648–658.
83. Axdorph U, Sjoberg J, Grimfors G, et al. Biological markers may add to prediction of outcome achieved by the International Prognostic Score in Hodgkin's disease. *Ann Oncol.* 2000;11:1405–1411.
84. Bashour CA, Yared JP, Ryan TA, et al. Long-term survival and functional capacity in cardiac surgery patients after prolonged intensive care. *Crit Care Med.* 2000;28:3847–3853.
85. Chung SH, Chu WS, Lee HA, et al. Peritoneal transport characteristics, comorbid diseases and survival in CAPD patients. *Perit Dial Int.* 2000;20:541–547.
86. Dharmarajan T, Sipalay M, Shyamsundar R, et al. Co-morbidity, not age predicts adverse outcome in *Clostridium difficile* colitis. *World J Gastroenterol.* 2000;6:198–201.
87. Dhiman RK, Makharia GK, Jain S, et al. Ascites and spontaneous bacterial peritonitis in fulminant hepatic failure. *Am J Gastroenterol.* 2000;95:233–238.
88. Gerhards MF, van Gulik TM, de Wit LT, et al. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma—a single-center experience. *Surgery.* 2000;127:395–404.
89. Moon KH, Song IS, Yang WS, et al. Hypoalbuminemia as a risk factor for progressive left-ventricular hypertrophy in hemodialysis patients. *Am J Nephrol.* 2000;20:396–401.
90. Nair S, Hertan H, Pitchumoni CS. Hypoalbuminemia is a poor predictor of survival after percutaneous endoscopic gastrostomy in elderly patients with dementia. *Am J Gastroenterol.* 2000;95:133–136.
91. Oki I, Tanihara S, Ojima T, et al. A multicenter collaborative study on the risk factors of cardiac sequelae due to Kawasaki disease: a one-year follow-up study. *Acta Paediatr.* 2000;89:1435–1438.
92. Sharma AP, Gupta A, Sharma RK, et al. Does serum albumin at start of continuous ambulatory peritoneal dialysis (CAPD) or its drop during CAPD determine patient outcome? *Adv Perit Dial.* 2000;16: 119–122.
93. Tanna MM, Vonesh EF, Korbet SM. Patient survival among incident peritoneal dialysis and hemodialysis patients in an urban setting. *Am J Kidney Dis.* 2000;36:1175–1182.
94. Yeun JY, Levine RA, Mantadilok V, et al. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis.* 2000;35:469–476.
95. Cueto-Manzano AM, Quintana-Piña E, Correa-Rotter R. Long-term CAPD survival and analysis of mortality risk factors: 12-year experience of a single Mexican center. *Perit Dial Int.* 2001;21:148–153.
96. Gulati S, Stephens D, Balfe JA, et al. Children with hypoalbuminemia on continuous peritoneal dialysis are at risk for technique failure. *Kidney Int.* 2001;59:2361–2367.
97. Kalantar-Zadeh K, Kopple JD, Block G, et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis.* 2001;38:1251–1263.
98. Leung HB, Ho YC, Carnett J, et al. Diabetic foot ulcers in the Hong Kong Chinese population: retrospective study. *Hong Kong Med J.* 2001;7:350–355.
99. Rozzini R, Sabatini T, Trabucchi M. Prediction of 6-month mortality among older hospitalized adults. *JAMA.* 2001;286:1315–1316.
100. Scott JD, Forrest A, Feuerstein S, et al. Factors associated with postoperative infection. *Infect Control Hosp Epidemiol.* 2001;22: 347–351.
101. Tokars JI, Light P, Anderson J, et al. A prospective study of vascular access infections at seven outpatient hemodialysis centers. *Am J Kidney Dis.* 2001;37:1232–1240.
102. Tveit DP, Hypolite I, Bucci J, et al. Risk factors for hospitalizations resulting from pulmonary embolism after renal transplantation in the United States. *J Nephrol.* 2001;14:361–368.
103. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA.* 2001;285:2987–2994.
104. Bakewell AB, Higgins RM, Edmunds ME. Quality of life in peritoneal dialysis patients: Decline over time and association with clinical outcomes. *Kidney Int.* 2002;61:239–248.
105. Klassen PS, Lowrie EG, Reddan DN, et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 2002;287:1548–1555.
106. Modawal A, Candadai NP, Mandell KM, et al. Weaning success among ventilator-dependent patients in a rehabilitation facility. *Arch Phys Med Rehabil.* 2002;83:154–157.
107. Sezer S, Özdemir FN, Arat Z, et al. The association of interdialytic weight gain with nutritional parameters and mortality risk in hemodialysis patients. *Ren Fail.* 2002;24:37–48.
108. Stefoni S, Cianciolo G, Donati G, et al. Low TGF-β1 serum levels are a risk factor for atherosclerosis disease in ESRD patients. *Kidney Int.* 2002;61:324–335.
109. Tincani E, Mazzali F, Morini L. Hypoalbuminemia as a risk factor for over-anticoagulation. *Am J Med.* 2002;112:247–248.

110. Wong CS, Hingorani S, Gillen DL, et al. Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. *Kidney Int.* 2002;61:630–637.
111. McMurray L-G, Roe JH, Sweet LK. Plasma protein studies on normal newborn and premature infants. I. Plasma protein values for normal full term and normal premature infants; II. Use of concentrated normal human serum albumin in treatment of premature infants. *Am J Dis Child.* 1948;75:265–278.
112. Smith CA, Phillips KG, Roth RO. Effects and fate of human serum albumin administered intravenously and orally to premature infants. *J Clin Invest.* 1950;29:218–226.
113. Ford EG, Jennings LM, Andrassy RJ. Serum albumin (oncotic pressure) correlates with enteral feeding tolerance in the pediatric surgical patient. *J Pediatr Surg.* 1987;22:597–599.
114. Brown RO, Bradley JE, Bekemeyer WB, et al. Effect of albumin supplementation during parenteral nutrition on hospital morbidity. *Crit Care Med.* 1988; 16:1177–1182.
115. Foley EF, Borlase BC, Dzik WH, et al. Albumin supplementation in the critically ill. A prospective, randomized trial. *Arch Surg.* 1990; 125:739–742.
116. Kanarek KS, Williams PR, Blair C. Concurrent administration of albumin with total parenteral nutrition in sick newborn infants. *JPEN J Parenter Enteral Nutr.* 1992;16:49–53.
117. Wojtysiak SL, Brown RO, Roberson D, et al. Effect of hypoalbuminemia and parenteral nutrition on free water excretion and electrolyte-free water resorption. *Crit Care Med.* 1992;20:164–169.
118. Golub R, Sorrento JJ Jr, Cantu R Jr, et al. Efficacy of albumin supplementation in the surgical intensive care unit: a prospective, randomized study. *Crit Care Med.* 1994;22:613–619.
119. Rubin H, Carlson S, DeMeo M, et al. Randomized, double-blind study of intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition. *Crit Care Med.* 1997;25:249–252.
120. Krauer B, Dayer P, Anner R. Changes in serum albumin and α_1-acid glycoprotein concentrations during pregnancy: an analysis of fetal-maternal pairs. *Br J Obstet Gynaecol.* 1984;91:875–881.
121. Blunt MC, Nicholson JP, Park GR. Serum albumin and colloid osmotic pressure in survivors and nonsurvivors of prolonged critical illness. *Anaesthesia.* 1998;53:755–761.
122. Emerson TE, Jr. Unique features of albumin: a brief review. *Crit Care Med.* 1989;17:690–694.
123. Zoellner H, Hou JY, Lovery M, et al. Inhibition of microvascular endothelial apoptosis in tissue explants by serum albumin. *Microvasc Res.* 1999;57:162–173.
124. Mimoz O, Soreda S, Padoin C, et al. Ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminemia: a model to explore the effects of decreased protein binding capacity on highly bound drugs. *Anesthesiology.* 2000;93:735–743.
125. Brown JM, Beehler CJ, Berger EM, et al. Albumin decreases hydrogen peroxide and reperfusion injury in isolated rat hearts. *Inflammation.* 1989;13:583–589.
126. Strubelt O, Younes M, Li Y. Protection by albumin against ischaemia- and hypoxia-induced hepatic injury. *Pharmacol Toxicol.* 1994;75:280–284.
127. Soejima A, Matsuzawa N, Miyake N, et al. Hypoalbuminemia accelerates erythrocyte membrane lipid peroxidation in chronic hemodialysis patients. *Clin Nephrol.* 1999;51:92–97.
128. Wu TW, Wu J, Li RK, et al. Albumin-bound bilirubins protect human ventricular myocytes against oxyradical damage. *Biochem Cell Biol.* 1991;69:683–688.
129. Greenough A, Emery E, Hird MF, et al. Randomised controlled trial of albumin infusion in ill preterm infants. *Eur J Pediatr.* 1993;152: 157–159.
130. Quinlan GJ, Margarson MP, Mumby S, et al. Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion. *Clin Sci (Colch).* 1998;95:459–465.